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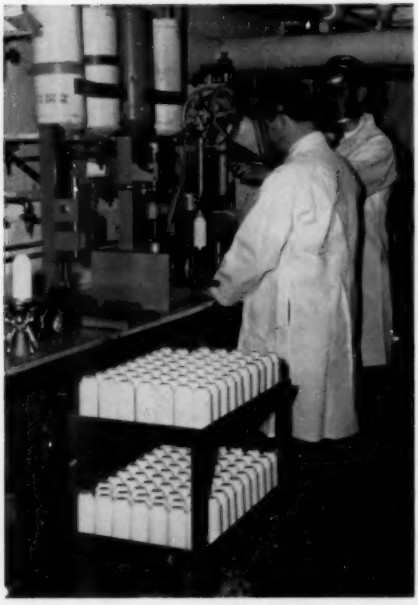

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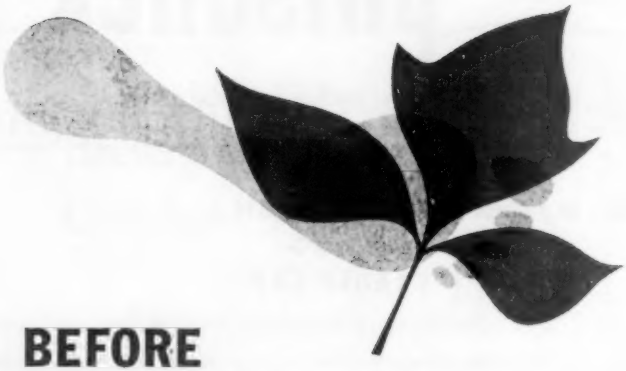

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AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

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CONTENTS

E D I T O R I A L

WASTING OUR HERITAGE

THE recent and successful efforts to have our importations of crude oil limited in order to increase the demand and use of domestic supplies must seem appalling to one who is a conservationist. While we do not presume to recognize all of the reasons and implications involved in this decision, we suspect that self-interest on the part of certain domestic oil producers had much to do with it. The argument advanced; namely, that it was vital as a means of maintaining our military preparedness, seems to us like a good smoke screen and one used only too often today as a means of gaining some objective.

Earlier this year, we read a brilliant address by Rear Admiral H. G. Rickover given at the Awards Banquet of the Sixteenth Annual Science Talent Search in Washington. Admiral Rickover has gained world-wide recognition for his brilliant and logical thinking and this address was an outstanding example of his brilliance. It should be read by every person in the United States. Quite unlike what one might expect from a military man, Admiral Rickover gave some astonishing facts and figures showing how this nation is depleting its natural resources. He views our future as largely dependent on the marshalling of outstanding brain-power in order to compensate for the eventual loss of our natural resources.

The figures given by Admiral Rickover are alarming and should cause concern even to the incorrigible optimists with which this country is blessed—or cursed. For example, in the U. S. alone, we have consumed as much irreplaceable mineral and fuel resources since 1914 as had been used by all the world in the previous five thousand years! With but ten per cent of the population of the free world and but eight per cent of its land area, we consume close to one-half the free world's volume of materials.

Oil is one of the things which the U. S. consumes in a larger amount than the rest of the world put together, and it is surely one

thing which—when it is gone—cannot be replaced. It is difficult to imagine how our nation could even survive without the huge quantities of oil necessary to keep our industrial machines running, our automobiles on the road, and our homes warmed. Had we not stepped into the breach during the recent cutoff of Middle East oil, the whole economy of the Western World would have collapsed and, with it, the Western Alliance. This is probably the very argument used by those who feel that we must keep domestic production high as a guarantee against some similar episode. On the other hand, is there any reason to believe that our security some few generations hence will be any more certain and that these generations as yet unborn will have a lesser need for fuel than we have at present? Could it not be that in taking some of the drastic steps which we take today, we are setting the stage for the defeat or collapse of this country at the hands of some nation presently undreamed of as a conqueror? Who, for example, would have believed twenty years ago that the United States could be forced into a stalemate with a country like China and is it not possible that, in a few decades, we may be fighting for survival?

While, as we have said, we do not presume to know all of the angles, the sane thing to do would be to maintain our oil reserves as long as possible and conserve them for the time when we may not be able to purchase oil on the world market. The fact that we have no difficulty in buying abroad what we need now is no proof that this will always be so. Political considerations may someday prevent it. Furthermore, with our expanding economy—if in the next twenty-five years our progress is the same—we will require eighty per cent of total world production of raw materials. There is serious doubt that we shall be able to obtain such an amount and we may find that we shall be entirely dependent on the meagre amounts which remain here at home. It would be well for those in control of our nation's affairs to remember that it is our natural resources which have made this country great. There is no reason to believe that Americans are more brilliant or more capable than other peoples even including those on whom we confer the description "backward". We must conserve as much as possible this, our heritage, if we are not to meet future disaster.

L. F. Tice

THE STABILITY OF PACKAGED PHARMACEUTICALS AS RELATED TO GLASS CHEMICAL DURABILITY *

By S. V. Subrahmanyam and J. P. Majeske **

THE property most desirable in a glass container for storing parenteral and other medicinal preparations is its chemical resistivity. This property of resistance toward the corroding action of water, acids, alkalies and salts is the primary reason for its preference over competing materials. Unexpected and undesirable changes in appearance, odor and hydrogen ion concentration have been noted in the packaged contents. Flakes have developed in neutral saline solutions prepared for intravenous injections which further had become toxic because of changes in alkalinity. A proper chemical durability test that would readily distinguish acceptable glass for these preparations is understandable and highly desirable. Over the years a number of tests have been developed differing both in procedures and techniques but they fail to give basic information on this fundamental property of glass because of inattention to detail or glass composition. However, during the last thirty years many systematic studies were conducted on glasses resulting in a better understanding of the property of chemical durability. There is no single method available which can be acceptable for all types of glasses. For example: methods used for optical glasses are too mild for chemical resistant glasses.

The stability of a glass for a particular purpose is best determined by actual service or by exposing the glass to conditions simulating as nearly as possible those conditions that will be met in service. The methods most widely used for chemical resistant glass and adopted by the U. S. P. are the Type I, Type II and Type III tests. These tests are performed on either powder samples or whole containers. The criterion for acceptability is titratable alkali.

This article will deal with a brief review of the existing knowledge of the structure of simple glasses, the action of various aqueous solu-

* Presented to the Conference on Preparation of Parenteral Products by the Hospital Pharmacist, April 27, 1957, N. Y. C.

** Associate Director and Director of Research, respectively, T. C. Wheaton Company, Millville, N. J.

tions on glass, the effect of inhibitors on the action of alkalies, the effect of composition on chemical durability and finally with the stability of medicinal formulations stored in glass containers.

II. Structure of Simple Glasses

In order to understand more clearly the action of various aqueous solutions on glass, a knowledge of the structure of glass is helpful. Container glass is composed of cations and anions held together by interatomic attractive forces. Oxygen is the only anion of importance and in most commercial glasses the volume contributed by oxygen to the glass is above 80%. The most common cations are silicon, aluminum, boron, sodium, potassium, calcium, magnesium, barium, zinc, etc. These cations are divided into three groups; those that participate in the building unit called the network formers and those that do not and are called network modifiers. In the most common glasses silicon and boron are the network formers. Alkaline metal and earth ions are network modifiers. To a third group, belong the intermediates, like aluminum, zinc, iron and probably titanium, which can participate in the net work or act as modifiers. The unit of structure in most commercial glasses is the silicon tetrahedron in which each silicon is surrounded by four oxygens and each oxygen is shared, in turn between two silicons. The tetrahedral groups are approximately fixed in position with respect to one another. However, beyond these spacings the net work is wholly random. The structure does not repeat itself identically at regular intervals, hence the material is not crystalline. Ions of alkali and alkaline earth metals occupy the holes or interstices in the network. With increasing amounts of these ions the continuity of the network is disrupted and when sufficient amounts have been added glass formation cannot be expected.

Boron, like silicon, is a glass former and when added to glass in amounts found in most container glass compositions result in a strengthening of the network. Aluminum and zinc may also participate in the network. When substantial amounts of alkali and alkaline earth ions are replaced by boron, aluminum or zinc a more chemically inert glass is obtained. For most purposes it would be ideal to have fused silica for glass containers but the difficulty of melting and fining coupled with its working properties make it too costly. In order to soften the glass and extend the working range

alkalies, alkaline earths, boron, zinc, aluminum, barium, etc., are added in varying amounts. The alkalies and alkaline earths are kept at a minimum to increase the chemical resistivity, as well as to prevent devitrification.

III. Action of Water, Acids, Alkalies and Inhibitors [1]

The action of aqueous solutions on glass is complex and should be considered not as a simple process of solution but as a reaction rate where time and temperature are extremely critical.

In the case of acid attack the concentration is of minor importance but the temperature at which glass is treated has a dominant influence. The reaction between the glass surface and attacking medium results in hydration and swelling. A look at the changes occurring in the glass surface when exposed to dilute aqueous solutions of acids and the properties of the silica gel so formed would be interesting. At the surface there will be a film of OH^- groups. The attack of acids and water is characterized by the hydrolysis of the Si-O-X bonds where X is either an alkali or an alkaline earth ion. In most cases X forms water soluble salts which are leached out, and hydrogen ion, probably with a water molecule attached, H_3O^+ takes its place. The resulting silica gel contains those Si-O-Si bonds which were originally present and a number of Si-OH groups. The ratio of Si-O-Si to Si-OH groups depends upon the basicity of the glass. The nature of the resulting silicic acid film is a function of the composition of glass. The affinity of the OH^- groups for water is responsible for the hydration and swelling of silica gel which forms when glasses are leached with acids. In addition to the hydration and dehydration of the silica gel, the silica gel is also undergoing an irreversible process called aging. Whenever the Si-OH groups react with the liberation of water, a strong Si-O-Si bond is formed which draws two SiO_4 groups closer together. This process takes place at room temperature but can be hastened by baking. The reaction of soda lime glass with acids can be treated as base exchange. The sodium and calcium ions are replaced by hydrogen ions or hydronium ions but the Si-O-Si bonds are not noticeably effected. The action of acids is governed by diffusion process.

Alkaline solutions react differently. The addition of NaOH breaks the existing Si-O-Si bonds by forming Si-O Na and Si-OH

units. The alkali attack leads to complete destruction of the glass surface and no film of reaction product is formed. The uppermost layer of glass is dissolved completely and a new surface of identical composition is created. As soon as four oxygens surrounding a silicon have been separated from the adjacent SiO_4 tetrahedra, the resulting SiO_4 island is detached and enters the solution. When glasses are exposed to acids, an improvement of the resistivity of the glass surface may result but no such effect can be expected from alkalies.

Inhibitors

In the action of alkaline solutions certain ions, even if present in extremely small concentrations (few mg. in a liter) exert a poisoning influence on the reaction. Hydroxides of calcium, zinc and aluminum retard the rate of reaction. These can be termed as negative catalysts. In order to become a negative catalyst the ion has to be adsorbed on the glass surface and form an easily soluble compound under the pH conditions prevailing at the glass surface. The tendency to be adsorbed increases with the positive field strength of the cation, it is weak for monovalent ions, strong for calcium and still more so for aluminum, zirconium and titanium. The optimum efficiency of a negative catalyst depends not only on the adsorption of the cation but also on its inertness toward alkalies. ThO_2 will not form a compound with alkalies, while Al_2O_3 will lose its inhibiting power if strong alkaline solutions are used.

IV. Compositions

Commercial Glasses:

Some typical compositions of borosilicate and soda lime glasses are presented in Table I. The borosilicate glasses (Type I), compared to soda lime, contain larger amounts of alumina, boric oxide, varying amounts of BaO and ZnO and relatively smaller amounts of alkali. An exception to the general borosilicate glass compositions is Pyrex which contains a very high amount of silica and a substantial amount of boric oxide but very small amounts of alumina and alkali. The Jena composition contains relatively large amounts of alumina and calcium oxide. In general, Type I colorless glasses contain SiO_2 from 66 to 74%, Al_2O_3 from 4 to 10%, R_2O from 8 to 10%, B_2O_3 from 9 to 12%, BaO from 0 to 3.5%, CaO from 0 to

3% and small amounts of ZnO and vanishingly small amounts of Fe_2O_3, Cl_2 and As_2O_3.

In the case of Type I amber glasses large additions of coloring agents are necessary to get the desired color. Certain difficulties are

TABLE I

TYPICAL COMPOSITIONS OF BOROSILICATE GLASSES

	Type I	Tubing	Amber	Container	Type
SiO_2	81.0	74.3	69.4	71.0	69.2
B_2O_3	12.5	13.0	12.7	5.0	10.7
Al_2O_3	2.4	4.6	6.0	3.2	2.0
Na_2O	3.5	4.2	7.4	7.8	4.0
K_2O	0.4	0.5	2.7	1.8	1.2
CaO	—	0.5	1.9	0.8	2.6
MgO	—	0.4	1.6	—	0.3
SO_3	—	2.0	—	2.0	—
Cl_2	—	—	—	0.4	—
Fe_2O_3	—	—	0.2	—	—
As_2O_3	—	—	0.2	—	—

TYPES AND COMPOSITIONS OF SOME LIMED GLASSES

SiO_2	72.5	72.0
B_2O_3	3.5	2.0
Al_2O_3	2.5	2.5
Na_2O	15.0	15.5
K_2O	0.5	0.5
CaO	5.0	5.0
MgO	1.0	1.0
SO_3	0.3	—
Cl_2	—	0.3

encountered in the melting of such glasses thus necessitating a higher alkali and lower silica content compared to Type I colorless glasses. The most common coloring oxides are Fe_2O_3, MnO_2 and TiO_2, the total ranging from 3 to 6%.

The soda lime glasses, which will be called Type III contain relatively higher percentages of alkali, from 13 to 16%, higher CaO and MgO, from 10 to 14%, SiO_2 from 69 to 73%, lower in Al_2O_3, from 0.5 to 2.5% and minor additions of BaO and B_2O_3. Type III amber glasses fall within the same range of composition as the Type III flints, except the alkali metal is slightly higher and earth ions somewhat lower.

Type II glasses have the same composition as the Type III glasses. However, the surface resistivity is increased by reaction of the surface alkali with acidic gases at elevated temperatures. A typical example of this is as follows:

$$Na_2O + SO_2 + \tfrac{1}{2} O_2 = Na_2SO_4$$

The bottles on emerging from the lehr have a white deposit of Na_2SO_4 which is highly water soluble.

Effect of Composition:

A great deal of information is available on the effect of composition on chemical durability. In simple sodium silicate glasses, increasing CaO increased the durability more than BaO or PbO (3). In the case of soda lime and soda magnesia glasses, MgO glasses were found to be better for water, showed no superiority for acid attack and were inferior toward alkaline attack. Replacing Na_2O by Al_2O_3, ZrO_2 or TiO_2 in a trisilicate glass, Turner and his Associates found effective increase in chemical durability. When ZrO_2 replaced SiO_2 they found the glasses had excellent resistivity against attack by water, HCl, Na_2CO_3 and NaOH (4). Peddle found a maximum durability in glasses containing Na_2O and K_2O in the ratio of 3:7 (5). Sen and Tooley found maximum durability in glasses when K_2O was 13% and Na_2O 5% in simple soda lime glasses (6). Gupta and Hess found that by introducing CaO for SiO_2 in simple alkali silicate glasses, the chemical durability of the potash glasses was improved much more than soda glasses (7).

Working with BaO-TiO_2-SiO_2 glasses (alkali free) Cleek and Hamilton (8) reported the chemical durability of these glasses to be

2% and small amounts of ZnO and vanishingly small amounts of F_2, Cl_2 and As_2O_3.

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TYPICAL COMPOSITIONS OF BOROSILICATE GLASSES

	Pyrex	*Tubing*	*Amber*	*Container*	*Jena*
SiO_2	80.63	74.54	66.48	71.20	66.52
Al_2O_3	2.18	5.52	7.27	5.40	10.47
B_2O_3	12.84	9.46	8.63	10.20	8.41
Na_2O	3.53	6.42	7.46	7.90	8.61
K_2O	0.41	0.58	2.17	1.30	0.22
CaO	—	0.87	1.93	0.60	5.45
MgO	—	0.14	1.46	—	0.19
BaO	—	2.30	—	3.00	—
ZnO	—	—	—	0.40	—
Fe_2O_3	—	—	2.19	—	—
MnO_2	—	—	2.05	—	—

TYPICAL COMPOSITIONS OF SODA LIME GLASSES

	Flint	*Amber*
SiO_2	71.52	71.10
Al_2O_3	1.85	2.61
Na_2O	12.76	14.85
K_2O	0.28	0.50
CaO	8.90	9.20
MgO	2.90	1.00
BaO	0.25	0.45
B_2O_3	0.40	—
Fe_2O_3	—	0.14

encountered in the melting of such glasses thus necessitating a higher alkali and lower silica content compared to Type I colorless glasses. The most common coloring oxides are Fe_2O_3, MnO_2 and TiO_2, the total ranging from 3 to 6%.

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Working with BaO-TiO_2-SiO_2 glasses (alkali free) Cleek and Hamilton (8) reported the chemical durability of these glasses to be

excellent and far superior to any of the known glasses for both acid and alkaline attack, the resistivity being even better than Pyrex and fused silica glass.

Turner and his Associates (9), in an extended survey of commercial glass compositions, came to the conclusion that the resistance to attack by boiling water for glasses having high SiO_2 content (especially those containing B_2O_3) were superior while inferior glasses were obtained with high alkali content. Continued treatment with water tended to improve the surface of glass. The action of acids closely paralleled that of water. In the case of action of alkalies they found the high borosilicates tended to rank below the high lime glasses. Tarnpoll and Junge (10) found that the rate and extent of attack increased when plate glass was treated with 5% solutions in the order indicated: KOH, K_2CO_3, NaOH, $Na_4P_2O_7$ and Na_2CO_3. Bacon and Burch (11) on an extensive survey of Type III commercial glasses found difficulties in attempting to correlate accelerated tests with actual performance of the bottles towards various solutions under service conditions. They found no relation between the amount of alkali leached and the tendency of the bottle to flake when filled with distilled water. In the case of alcoholic solutions, it was found that as the alcoholic content increased the attack on glass decreased generally, flaking also decreased as the alcoholic content increased (12).

V. Stability of Formulations

Preparations in glass containers should not change color, odor, potency or pH. An ideal glass for pharmaceutical houses would be a truly neutral glass; a glass surface that would not send alkali ions into solution and remain unaffected under all pH conditions and above all show no flaking on continued storage. The present tendency to package drugs of high potency and thus small dosage, demands a glass of high durability. Even small changes in concentration may mean considerable drop in potency. Drugs sensitive to pH variation may be particularly affected.

The British Pharmacopoeia in 1953 recognized the use of treated soda lime containers (Type II) but cautioned against indiscriminate use. The life of the resistant veneer depends upon a number of factors, including conditions of storage, temperature, detergents and packaged contents, to mention a few. The original highly alkaline

surface is again exposed when the resistant veneer is destroyed. Based on unpublished work performed at the T. C. Wheaton Co., it appeared to indicate that Type I borosilicate was only slightly affected by elevated temperatures or by prolonged treatment in the autoclave. Similarly, commercial detergents as tested had no effect on the surface durability of Type I glass, while the resistant veneer of Type II glass was made ineffectual or eliminated under the same conditions.

Some of the factors that influence the degree of glass contamination are—

1. Glass composition.
2. Nature of liquid.
3. Temperature.
4. Duration of contact.
5. Concentration of solution.
6. Relation of container surface and of liquid.
7. Previous thermal history.
8. Storage conditions.

It is common to package distilled water for later use in preparing solutions for injection. The quality of such water is specified by its pH and residue left on evaporation. Greene and his Associates (2) stored ampules of distilled water for a period of two years with and without preliminary autoclaving. Solids picked up by water were found in most cases to increase steadily for the duration of the storage period, while the pH tended to reach a constant value, characteristic for each glass.

Base exchange reactions occur at room temperature between glass and aqueous solutions. Special attention has to be taken in micro analytical work where compositions changes occur in the glass reaction vessels. The adsorption of H^+ and release of Na^+ in certain medicinal preparations may be of major consideration. Alkali released from glass may catalyze many organic reactions. Glassware cleaned with the usual chromic acid solution results in adsorption of chromium ions on the glass surface and in turn are slowly released when subsequently used. They were found to be determined on yeast, several species of spirogyra and other low forms of life (1). Base exchange reactions releasing silver ions into solutions from treated glass had an effect on bacteria coli (1).

Solutions of alkaloids are especially sensitive to alkali such as Apomorphine, Atropine, Morphine Muriate, Narcotine Hydrochloride, etc. Only such glass as will not cause decomposition,

crystallization or turbidity should be used. According to Tilman & Midner (13) some of the troubles encountered in the preparation of salvarson solutions originate from the extracted alkali. In some cases it was suspected as causing death due to alkalies dissolved from glass.

Flake Formation:

Flaking is a very serious problem in stored solutions. It can be observed when citrates, tartrates and saline solutions are stored in glass containers. Bottles on extended storage tests gave lower alkali than new containers. However, more flakes occurred during extended storage. Sodium citrate and phosphate always cause flaking in a short time. The flakes appear at times under light illumination as brilliant irridescent particles of various shapes and sizes ranging from several mm. to 0.001 mm. Insoluble decomposed glass at times appears as a flocculent precipitate. Autoclave treatment at high temperature hastens their formulation. Injection or ingestion of contaminated medicinal solutions may cause pathological effects. Stantial & Dolan (14) in a study of silicosis gave intravenous injections to dogs containing silica who died subsequently. Gardner & Cummings (14) subjected rabbits to intravenous injections of silica particles of various sizes. The smallest particles caused grave disorders. Brewer & Dunning (15) (1947) reported their results of the effect of *in vitro* and *in vivo* study of glass particles in ampules. The possibility of an embolism being caused by particulate glass was investigated. Frequent and concentrated injection of coarse particles were found to cause damage in various parts of the test animal body. However, when glass diluted to resemble normal contamination was used, after filtering of exceedingly large particles, no lesions were found and pathologists verified the entirely normal condition of the test rat. In another series of tests, the concentrate from ampules manufactured regularly and rejected for contamination by particles was injected with no cases of death or permanent damage. The authors, while admitting the need for a vigilant attitude towards possible damages caused by the injection of silicious material on the part of the ampule manufacturer, appear to believe that the manufacturer in general will not have to fear that a solution free from contamination to the naked eye will cause emboly even if occasional particles remain present. However, they point out that ultra fine

glass particles of less than one micron may cause pathological effects and should be guarded against. Although the authors express some optimism, based on their study, they concede inherent dangers in the contamination of glass particles.

The French Glass Institute, Medical and Public Authorities (1946) (16) studied, in aqueous media, the formation and nature of flakes as a function of glass composition. Leached alkali was not considered the essential phenomenon. The composition of glasses studied are presented in Table 2.

TABLE 2

	A	*B*	*D*	*E*
SiO_2	71.4	70.2	77.5	71.0
B_2O_3	3.4	1.4	6.0	1.0
Al_2O3) Fe_2O_3)	8.4	8.1	4.8	3.0
BaO	—	—	3.6	—
CaO	2.0	3.9	0.3	4.0
MgO	0.6	1.1	0.2	1.0
ZnO	2.5	2.3	—	2.0
Na_2O) K_2O)	10.7	12.8	7.4	17.0
Misc.	0.1	0.2	0.2	1.0

Ampuls of 30-35 ml. capacity and 13 mm. in diameter were selected and autoclaved at temperatures of 145-150° C. Using double distilled water they found flakes were present after fifteen hours in "A", two hours in "B", none in "D" and in two hours in "E". Silica was present in all solutions having flakes. Using a N/1000 solution of NaOH flake formation was greatly accelerated. Glass "A" flaked in 1½ hours, glass "D" showed no flakes. The results were comparable to N/1000 NaOH using a 0.05 molar solution of borax. A N/1000 solution of baryta promoted turbidity but caused no flakes. Sodium silicate in very dilute form appeared to prevent flake formation. Likewise Urotropin (Hexamethylene-tetramine) in 5 to 10% concentration prevented flake formation. Using N/100 HCl no flakes were found in "B" in three hours. The amount of alkali leached was only a third

as when water was used. The acid tested ampules were washed and retested with water for eight hours. No flake formation was noticed. CO_2 contaminated distilled water extended the time for flake formation. Based on chemical analysis, the composition of flakes and dissolved matter for glass "B", which appeared to be the worst offender among the four glasses, is presented in Table 3.

TABLE 3

	Hydrated Weight Percent	*Ignited Weight Percent*	*Comp. of Dissolved Matter*
SiO_2	35.0	42.6	67.0
B_2O_3	0.0	0.0	1.4
Al_2O_3) Fe_2O_3)	18.5	22.6	6.5
CaO	2.5	3.1	3.7
MgO	3.0	3.7	0.9
ZnO	10.5	12.8	1.4
Alkali	12.5	15.2	11.6
Ignition Loss—750° C.	18.0		

It is evident from the above table that the flakes contain a higher percentage of alumina, zinc oxide, magnesium oxide and slightly higher alkali and relatively lower silica compared to the parent glass composition. There appears to be a preferential breakdown of bonds when flake formation occurs. The ratio of material in solution to the weight of flakes was found to be 13:1 or more specifically total dry extract from 100 ml. test solution amounted to 1.8 mg. of flakes to 23.2 mg. of soluble material.

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TESTING FOR STERILITY OF CORN OIL

Part I

Dispersion of Spores in Corn Oil and in Saline *

By Kenneth E. Avis ** and Louis Gershenfeld ***

Preface

PHARMACEUTICAL preparations are frequently supplied in oleaginous vehicles. Such preparations are used at times under conditions which require them to be sterile. Oil for parenteral use is such a vehicle and must, therefore, meet the U. S. P. test for sterility for liquids.

A search of the literature has shown that a limited amount of data is available concerning liquid oleaginous vehicles of pharmaceutical interest which must be sterile. Frequently, the results which have been published as a result of studies by different authors were contradictory or inconclusive.

The opinion is prevalent that vegetative forms of bacteria will not survive for more than brief periods of time in an anhydrous oleaginous system. However, it has been shown that certain vegetative forms of bacteria will survive and remain viable for at least a few weeks and spores will remain viable for at least several months (1, 2, 3).

It has been proposed by various authors that oils may be sterilized by means of bacteria-excluding filters, by dry heat, and by means of steam. A review of the available literature reports on sterilization procedures for oils has been presented by the authors in connection with two previous reports. One study reported the results of an investigation of the effectiveness of bacteria-excluding filters with

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oils (4) and the other reported an investigation of the time required for various volumes of oil to reach the temperature of a sterilizing chamber when either hot air or steam was the source of heat (5).

From the foregoing literature survey, it became evident that much data was needed to provide confidence concerning the obtaining of sterility of liquid oleaginous materials and, also, in the testing for the sterility of such materials. In addition to the official U. S. P. method for determining the sterility of oils, two other procedures have been used by others. One of these procedures has been a filtration method (6, 7, 8). In this method, an asbestos filter pad was used as the filter medium and then the entire pad was placed in culture medium and incubated. The other procedure has been that of emulsifying a sample of the oil and then culturing an inoculum of the emulsion. Such a method was reported in an unpublished thesis (9).

It was deemed advisable to learn the nature of present pharmaceutical practice. Therefore, a letter was sent to 59 American manufacturers of parenteral products requesting answers to the following questions, among others:

1. (a) Do you use the U. S. P. and N. F. sterility tests (as is) for examining oils and oleaginous material?

(b) If yes, do you approve of these procedures?

2. If your answer to No. 1(a) is no, what technique do you use?

Replies were received from 52 manufacturers, an 88 per cent response. Several of those who did respond did not answer all of the questions. Of the 37 who answered No. 1, 29 indicated that they did use the official sterility test, but 15 of 27 indicated that they did not approve or have confidence in the offical test. The techniques indicated in answer to question No. 2 were essentially various modifications of the official U. S. P. technique with the addition of emulsifying agents to emulsify the oil inoculum.

Introduction

The following study of the sterility testing of oils, largely corn oil, is presented in three parts. Part I is concerned with the dispersion and recovery of the spores of *Bacillus cereus* ATCC No. 7064 in

sterile corn oil. This dispersion was used subsequently in sterility testing methods. Part II deals with sterility testing methods employing filters and filtration procedures, and Part III with sterility testing methods employing culture tube inoculation procedures and nonionic surfactants.

Before Part II and Part III could be carried out, a method of recovery of spores was necessary. In order to adequately evaluate such a procedure, the number of spores present in a given volume of oil had to be known with a reasonable degree of accuracy. The difficulty of accomplishing reproducibility of recovery of organisms, even in aqueous solutions, from surfaces on which they have been dried, has been encountered in studies of the effectiveness of disinfection of surfaces. One report (10) indicated that a variation of as much as 40 fold in the number of bacterial cells recovered at different times from a stainless steel surface was encountered. Another report (11) indicated that the recovery of spores varied markedly with the nature of the surface and of the rinsing liquid.

Reports have been given (1, 8) on the distribution of spores and vegetative forms of microorganisms in oils. The technique employed involved spray-drying the spores or vegetative forms in the presence of peptone or stearin. The powder thus obtained was milled and a weighed quantity was dispersed in sterile oil by trituration in a sterile mortar. The test spores were dispersed and recovered quite efficiently, as determined by a solvent extraction procedure, the vegetative forms less so.

In view of the above findings, the following study was undertaken. Inasmuch as the recovery of spores from oils is not always possible and the evidence of effective dispersion and of the recovery of spores are so inter-related, initial dispersion studies were undertaken using saline as the dispersing vehicle. Information thus gained might be applicable to the use of corn oil as the dispersing agent.

Methods

Initially, a method previously reported (9) was employed in this study. The method consisted of drying by incubation a suspension of the microorganisms on a weighed quantity of sand. The organisms were then dispersed in sterile oil by shaking. In the study reported herein, the obtaining of growth in tubes of fluid media inoculated with corn oil treated by this sand dispersion method was

erratic. In addition, the grains of sand moved very sluggishly when shaken in the oil and, occasionally, small grains of sand were drawn up inadvertently into the transfer pipette. The latter could be a source of variance in results. Consequently, a ball milling procedure was employed in most of the following work.

Spore Suspension

A spore suspension of *B. cereus* ATCC No. 7064 was prepared according to the procedure recommended by the Microbiological Section, A. M. A. Laboratories (12). The organism was incubated for 3 days or longer on trypticase soy agar slants at 30° C. The growth was then washed off with sterile saline (isotonic sodium chloride solution), centrifuged, the supernatant discarded, and then resuspended in sterile saline. The suspension was again centrifuged, the supernatant discarded, and then resuspended in sterile saline. This washed suspension was heated in a water bath for 30 minutes at 80° C. The spore suspension was then standardized by means of triplicate pour plates in trypticase soy agar medium (hereafter designated as TSA) and by filtration through Millipore filters. The spore suspension thus prepared was found to contain approximately 300,000,000 spores per ml. Dilutions of this suspension in sterile saline were prepared and then stored at 4° C. until used.

Measured volumes of these spore suspensions were placed in sterile test tubes (25 x 150 mm.) in an incubator at 30 to 32° C. until dried. Previously, there had been added to the test tubes a specific number of sterile 5 or 6 mm. glass beads or ½ inch porcelain balls. At the time of use, a measured volume of sterile saline or sterile corn oil was added aseptically to the test tubes. The tubes were then rotated for a timed interval, as indicated later. After the early portion of the study, a small volume (1 ml.) of sterile Tween 80[a], or sterile saline, or sterile corn oil was added initially to the test tubes. After preliminary rotation with this 1 ml. of liquid, an additional volume of sterile saline or sterile corn oil was added and the tube was again rotated.

Rotation was accomplished by one of two methods. The tubes were spun on their axes by means of pulley-driven, interleaved wheels geared to a motor so that the spinning occurred at a rate of about 80 r.p.m. See Figure 1. By the other method, the tubes were

[a] Supplied by Atlas Powder Co., Wilmington, Del.

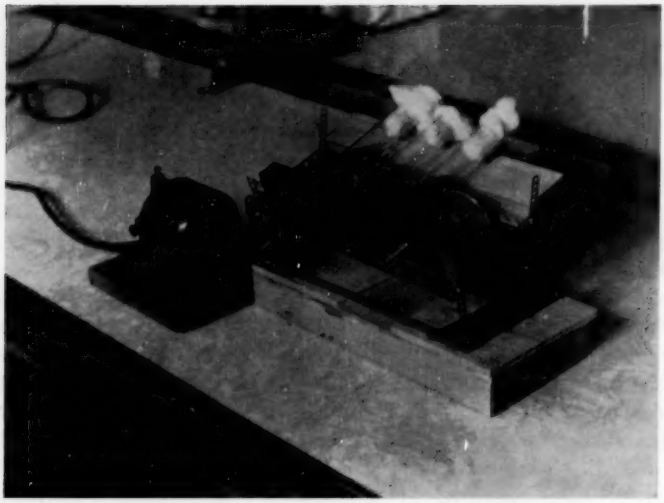

FIGURE 1

DEVICE FOR SPINNING CULTURE TUBES

rotated in a wheel provided with appropriate holes at a distance of about 5 inches from center. Rotation of the wheel occurred at a rate of about 25 r.p.m. by means of an electric motor. See Figure 2. Both of the above mechanisms were inclined so that the tubes rotated at about an angle of 15 degrees from horizontal.

Dispersion of Spores in Saline or Corn Oil

At the beginning of these controlled tests, it became evident that very few spores grew after an inoculum was transplanted. It was found, however, that by heating the suspension of spores in a water bath at 80° C. for a period of 3 to 6 minutes, a much higher recovery was obtained. This procedure is at times designated as heat shocking of spores.

Initially, 20 ml. or 30 ml. of sterile saline or sterile corn oil were added aseptically to the tubes containing the dried spores and the glass beads or porcelain balls. The tubes were then spun or rotated for one hour. After rotation was completed, the tubes were placed

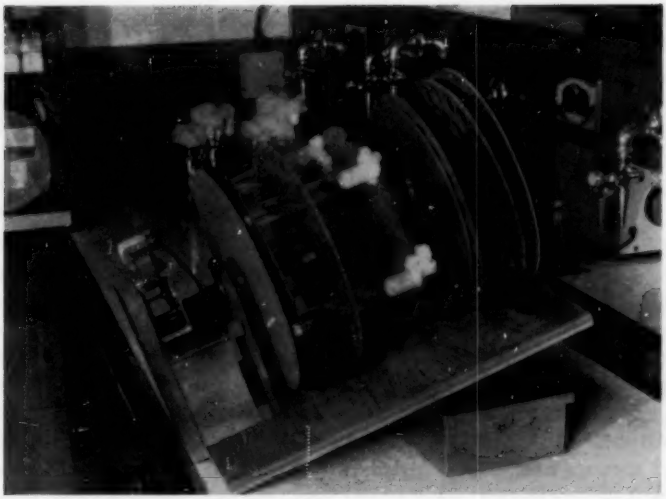

FIGURE 2

DEVICE FOR WHEEL ROTATION OF CULTURE TUBES

in a water bath at 80° C. for 3 to 6 minutes and then into cool water. Inocula were then removed by means of pipettes, which were also used for a final stirring of the liquid, and transferred to melted TSA. After mixing by shaking in sterile clean test tubes, the inoculated agar was poured into sterile Petri dishes. The plates were then incubated at 30 to 32° C. and examined after 24 to 48 hours and again after 5 to 7 days. Maximum growth normally occurred within 48 hours.

During rotation or spinning, it was noticed that the glass beads or porcelain balls rolled well in saline but tended to slide sluggishly in the corn oil. The latter condition was partially corrected by increasing the number of glass beads to a maximum of 10, using the 6 mm. instead of the 5 mm. glass beads or by using the ½ inch porcelain balls, and by employing 1 ml. of the dispersing liquid instead of the 20 or 30 ml. Another change in procedure was made in that the tubes were placed in a water bath at 80° C. for 1 to 3 minutes immediately before, rather than after, being spun or rotated.

Introducing the heat shocking of the spores at this point had the effect of also reducing the viscosity of the corn oil. The rolling of the glass beads and porcelain balls was improved by using the small volume of warmed liquid. After 5 to 15 minutes rotation with the small volume of liquid, additional sterile saline or corn oil was added to the tubes and the rotation continued for 15 to 90 minutes.

On the premise that a liquid miscible with both water and corn oil might aid in the dispersion of the spores in either liquid and, possibly, in subsequent recovery from the corn oil or saline, Tween 80, dioxane, and ethyl cellosolve were tried separately in volumes of 1 ml. as the initial dispersing liquid.

In an attempt to provide better control of the number of spores dispersed in saline or corn oil, 1 cm. squares of E & D #615 filter paper were soaked in spore suspensions of *B. cereus* and then dried at a temperature of 30 to 32° C. These were introduced into sterile test tubes (25 x 150 mm.) along with glass beads or porcelain balls and rotated with dispersing liquids as described. During rotation, it was observed that, particularly with the corn oil, the filter paper squares often floated above the rolling beads or balls and received very little milling effect from these objects. At times, they also clung to the wall of the test tubes above the milling objects.

Findings

The dispersion of spores of *B. cereus* in saline showed considerable variation from one experiment to another, as evidenced by colony counts in TSA plates inoculated with measured volumes of the saline suspension prepared. The data given in Table I show the effectiveness of spore dispersion, in terms of the percentage of the theoretical number, as evidenced by representative colony counts obtained in TSA plates. The theoretical number was the number of spores that were in the volume of standardized spore suspension which had been dried in the test tubes.

In Table I, representative data are recorded for the dispersion of spores from the walls of glass test tubes in saline by means of glass beads or porcelain balls as milling objects. Although there is a 5 to 10 fold variation in the number of spores dispersed, this compares favorably with the 40 fold variation previously referred to. Occasionally, an abnormally high plate count was obtained, probably due to the chance pick-up of a clump of spores in the inoculum.

The experiments indicated by "T" in Table I are those in which 1 ml. of Tween 80 was used as the initial dispersing liquid. It will be noted that a significantly larger percentage of spores were dispersed when Tween 80 was used as the dispersant, although there was still appreciable variation from one experiment to another in the percentage dispersed.

Data were obtained from the dispersion of spores in saline from 1 cm. squares of filter paper. In many of the experiments the variation in the number of spores obtained by plate counts from one experiment to another, with one type or number of milling objects, was within the same magnitude as that obtained when the spores were dispersed from the glass walls of test tubes. However, in some experiments the variation was much greater. These findings, together with poor results obtained from preliminary experiments in dispersing spores from filter paper squares in corn oil, led to the conclusion that

TABLE I

DISPERSION OF B. CEREUS SPORES IN SALINE (20 ML.) FROM GLASS TEST TUBE SURFACE

Spore Suspension		Dispersion Method	Percentage of Theoretical Number[a] of Spores Dispersed with	
Volume	Dilution		One ½ inch Porcelain Ball	Ten 5 mm. Glass Beads
1 ml.	1:10,000	wheel[c]	8	—[b]
		spin[d]	20	—
1 ml.	1:100	wheel	44	—
		spin	28	—
0.5 ml.	1:100	wheel	20	—
		wheel	50T	—
		wheel	4	—
		wheel	36T	—
0.1 ml.	1:100	wheel	35	50
		wheel	110T	110T

[a] The number of spores present in the standardized suspension dried in the test tubes.

[b] — = No data.

[c] Test tube in wheel 5 inches from center, traveling in circle at approximately 25 r.p.m.

[d] Axial rotation of test tube at approximately 80 r.p.m.

T = Initial rotation was with 1 ml. Tween 80.

effective dispersion of spores from filter paper squares in corn oil was not a dependable procedure.

Comparison of data from Table I, between the use of wheel rotation and spinning as the dispersion method, would indicate little advantage for either method. In some cases the spores were dispersed more effectively by spinning and in other cases by wheel rotation. Since neither method appeared to possess an advantage as to effectiveness, the wheel rotation method was used more frequently because more tubes could be handled at one time.

Table II shows representative data obtained when spores were dispersed in saline and in corn oil from the walls of glass test tubes. The results are expressed as percentage dispersed as compared with the theoretical number of spores that were present in the volume of original suspension dried in the test tubes. With both saline and corn oil dispersions, the effectiveness of dispersion was based upon the number of colonies obtained when inocula were transferred into pour plates of TSA and then incubated.

TABLE II

DISPERSION OF B. CEREUS SPORES IN SALINE AND IN CORN OIL FROM GLASS TEST TUBE SURFACE

Spore Suspension		Dispersion Method	Percentage of Theoretical Number[a] of Spores Dispersed with					
			One ½ inch Porc. Ball		Six 5 mm. Glass Beads		One ½ inch Porc. Ball, Two 6 mm. Glass Beads	
Volume	Dilution		in Saline	in Oil	in Saline	in Oil	in Saline	in Oil
0.1 ml.	1:100	wheel[b]	140T	33T	110T	11T	80	40T
		wheel	200T	32T	50	1	—[c]	8.3×10^{-4}
		wheel	—	45	—	—	—	—
		wheel	—	23	—	—	—	—
0.1 ml.	1:1000	wheel	—	1.7T	5T	1.7T	—	1.7T
		wheel	—	—	—	0.6	—	2.0T
		wheel	—	—	—	—	—	4.8×10^{-5}
		wheel	—	—	—	—	—	1.6×10^{-5}

[a] The number of spores present in the standardized suspension dried in the test tubes.

[b] Test tube in wheel 5 inches from center, traveling in circle at approximately 25 r.p.m.

[c] — = No data.

T = Initial rotation was with 1 ml. Tween 80.

It will be noted that the percentage of spores dispersed in saline was considerably greater than that dispersed in corn oil. Recovery of contaminants from oils is and always has been a difficult problem. On the other hand, effectiveness of dispersion can only be judged by the successful recovery of the spores.

In order to obtain a more uniform dispersion of spores in both saline and corn oil, suitable liquids miscible with both saline and corn oil were used as initial dispersants. One ml. volumes of Tween 80, dioxane, and ethyl cellosolve were used initially as dispersants during the first 5 minutes of rotation. Afterward, 19 ml. of saline or corn oil were added to each tube and the rotation continued for 15 to 90 minutes. In the case of dioxane and ethyl cellosolve, the number of spores recovered was less. Time did not permit determining whether this was due to ineffective dispersion or a possible bactericidal effect. On the other hand, it can be noted from Table II that Tween 80 increased the effectiveness of dispersion, as indicated by the recovery of spores from both saline and corn oil. However, it may have been that the Tween 80 in the corn oil made it possible for more of the spores to grow in the medium. Whatever the mechanism, the effect was that of an improvement in the apparent effectiveness of dispersion of the spores in corn oil. It will be noted that a very low percentage of recovery was obtained from all experiments in which the 1:1000 dilution of spore suspension was used. The reason for this is not certain.

The data recorded in Table II would also indicate that a ½ inch porcelain ball or a ½ inch porcelain ball and two 6 mm. glass beads were somewhat more effective in dispersing spores in corn oil, as well as in saline, than as many as six 5 mm. glass beads.

Several experiments were conducted to determine whether or not the length of time of rotation with a milling object had an effect on the dispersion of the spores. Inocula were removed from tubes at various intervals after 5 minutes to 90 minutes of rotation in the wheel. Dispersion in both saline and corn oil was employed both with and without Tween 80 as the initial dispersant. No significant difference was found in the number of spores dispersed after rotation for the various time intervals except, occasionally, if the period of rotation was only 5 minutes. Therefore, more than 5 minutes rotation should be employed. A typical example of the effect of time of rotation upon the plate counts from both saline and corn oil tubes may be noted in Table III.

TABLE III

DISPERSION OF B. CEREUS SPORES IN SALINE AND IN CORN OIL—THE EFFECT OF ROTATION TIME

Spore Suspension in 30 ml.	Inoculum Plated	Colony Count After Rotation for Five Minutes	Fifteen Minutes	Thirty Minutes	Sixty Minutes	Ninety Minutes
Saline[a]	0.1 ml. of 1:100 dilution	10	9	13	12	9
		18	18	22	16	18
Corn Oil[a]	0.01 ml.	—[b]	23	—	37	—
		—	24	—	29	—

[a] Dry spores in test tube from 0.1 ml. of 1:100 dilution rotated in wheel with one ½ inch porcelain ball. Initial rotation for 5 minutes with 1 ml. of Tween 80, then diluted to volume and above rotation started.

[b] — = No data.

Summary and Conclusions

Spores of *B. cereus* were dispersed in saline and in corn oil from the walls of glass test tubes or from 1 cm. squares of filter paper by milling with 5 mm. or 6 mm. glass beads or with ½ inch porcelain balls. Considerable variation was encountered in the number of spores dispersed. However, excluding a few findings which were obviously out of range, the variation in dispersion within one particular milling technique from glass surfaces in saline did not exceed about 10 fold, and was usually within 5 fold. From filter paper squares, the variation was within about the same magnitude for a majority of the experiments. However, the filter paper squares were not used for the dispersion of spores in corn oil after a few preliminary trials because of the poor results obtained.

Tween 80 aided the effective dispersion of spores in saline and also in corn oil from glass surfaces. A porcelain ball was somewhat more effective as a milling object than 5 mm. glass beads where six or less were used. Milling objects, either glass beads or porcelain balls, were definitely more effective than rotation without milling objects in the tubes. Spinning the tubes or rotating them in a wheel during milling was approximately equally effective. The length of time of rotation between fifteen and ninety minutes had no appreciable effect on the number of spores dispersed in either saline or corn oil. Using a ½ inch porcelain ball as the milling object and Tween 80 as the initial dispersant, about 1/3 to 1/6 as many spores were dispersed in corn oil as in saline, as noted by colony counts from inocula in TSA.

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ALKALOIDAL PLANTS OF THE APOCYNACEAE [1]

By J. J. Willaman * and B. G. Schubert **

ALTHOUGH there has always been a keen interest in alkaloids and in the plants which contain them, recently there has been a particular resurgence of interest, due largely to the medical uses of the *Rauvolfia* alkaloids. Alkaloid-bearing plants are now being sought more assiduously than ever. We are preparing as complete a compilation as possible of all plants in which alkaloids have been found. To our knowledge such a list has not been published. It should serve as a guide in the further exploration of the plant world.

Several people have already consulted the list for the Apocynaceae and, because of the current widespread interest in the alkaloids of this family, have urged that we publish our data on it in advance of the whole compilation. The compilation consists of two tables with certain spacesaving devices. In the first the plants are listed alphabetically. The alkaloids are listed by numbers which refer to table 2. The citations are given not to the original paper in most cases, but to the most generally accessible source where the original may be found. The plant names have of necessity been taken from the chemical literature. Some of them are no longer in good usage botanically. Without voucher specimens, however, adequate corrections cannot be made, and except for verification of spelling and authorities, the names must stand as the chemical workers gave them. The second table lists the named alkaloids alphabetically, with synonyms where necessary.

We have aimed to make the list complete through 1955 but have included the more accessible items of 1956. If readers know of gaps in the list, we would appreciate hearing from them.

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TABLE 1

RECORDED OCCURRENCE OF ALKALOIDS IN APOCYNACEAE. ALKALOID NUMBERS REFER TO TABLE 2. "UNN." MEANS UNNAMED

Code for references:

AJP —American Journal of Pharmacy.

BA —Biological Abstracts.

CA —Chemical Abstracts.

Chopra —Chopra, R. N., Badhwar, R. L. and Ghosh, S. Poisonous Plants of India. Vol. 1. Indian Council of Agricultural Research. Scientific Monograph No. 17. Manager of Publications, Delhi, 1949.

CI —Chemistry and Industry.

H —Henry, T. A. The Plant Alkaloids. Fourth Ed., 1949. Blakiston, Philadelphia.

Helv —Helvetica Chimica Acta.

JACS —Journal of the American Chemical Society.

JAPA —Journal of the American Pharmaceutical Association, Scientific Edition.

JCS —Journal of the Chemical Society (London).

JOC —Journal of Organic Chemistry.

Klein —Klein, G. Handbuch der Pflanzenanalyse. Vol. IV, 1933. Julius Springer, Jena.

Merck —Merck Index. Ed. 6, 1952. Merck and Co., Rahway, New Jersey.

M-H —Manske, R. H. F., and Holmes, H. L. The Alkaloids. Five vol., 1950-1955. Academic Press, New York.

Sok —Sokolov, V. S. Alkaloid Bearing Plants in U. S. S. R. Akad. Nauk SSSR, Moscow.

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Wall 363 —Wall, M. E., Krider, M. M., Krewson, C. F., Eddy, C. R., Willaman, J. J., Correll, D. S. and Gentry, H. S. Steroidal Sapogenins XIII. Supplementary Table of Data for Steroidal Sapogenins VII. AIC-363. 1954 (processed). U. S. Dept. Agr., Eastern Utilization Branch, Philadelphia.

We —Wehmer, C. Die Pflanzenstoffe. Second Ed., 2 vols., 1929, 1931. Fischer, Jena.

We Sup —Wehmer, C. Die Pflanzenstoffe. Ergänzungsband zur zweiten Auflage. 1935. Fischer, Jena.

Webb 232—Webb, L. J. Guide to the Medicinal and Poisonous Plants of Queensland Bull. 232. 1948. Council for Scientific and Industrial Research, Australia.

Webb 241—Webb, L. J. Australian Phytochemical Survey. Part I. Bull. 241. 1949. Commonwealth Scientific and Industrial Research Organization, Australia.

Webb 268—Webb, L. J. Australian Phytochemical Survey. Part II. Bull. 268. 1952. Commonwealth Scientific and Industrial Research Organization, Australia.

Webb PS—Webb, L. J. A Preliminary Phytochemical Survey of Papua-New Guinea. Pacific Science 9:430 (1955).

Code for plant parts:

b —bark
fr—fruit
l —leaves
r —root
rb—root bark
s —stem, twig
sd —seed
w —whole plant above ground
wd—wood

Species	Plant part	Alkaloids	References
Acokanthera abyssinica (Hochst.) K. Schum.	—	1	We 978
Alstonia actinophylla (Cunn.) K. Schum.	l, b	unn.	Webb 241
Alstonia angustiloba Miq.	b	44	H 716
Alstonia congensis Engl.	b	43	H 716
	b	44	CA 49:14266
Alstonia constricta F. Muell.	b	17, 18, 19, 84, 85	H 716
	rb	103	CA 49:16334
Alstonia gilletii DeWild.	b	44	H 716
Alstonia macrophylla Wall.	b	72, 73, 122	H 716
Alstonia muelleriana Domin	b, l	unn.	Webb 268
Alstonia scholaris (L.) R. Br.	b	42, 43, 44, 45	H 716
	—	19, 84	Sok 129
Alstonia sericea Blume	l, b	unn.	We 985
Alstonia somersetensis F. M. Bailey	b	72, 122	H 716
Alstonia spatulata Blume	b	44	H 716

Species	Plant part	Alkaloids	References
Alstonia spectabilis R. Br.	b	16a, 42, 44, 45	H 716
Alstonia verticillosa F. Muell.	b	44	H 716
Alstonia villosa Blume	b	122	H 716
	b	44	JCS 1932:2626
Alstonia spp.	—	unn.	Webb PS
Alyxia ilicifolia F. Muell.	l	unn.	Webb 268
Alyxia ruscifolia R. Br.	l, fr	unn.	Webb 241
Alyxia stellata Roem. and Schult.	b	unn.	We 988
Alyxia sp.	l	unn.	Webb 241
Amsonia ciliata Walt.	w	unn.	Wall 363
Amsonia elliptica (Thunb.) Roem. and Schult.	r	20	CA 45:1730
Amsonia tabernaemontana Walt.	sd	114	CA 49:9670
Aspidosperma album (Vahl) Benoist	b	unn.	CA 48:13958
Aspidosperma australe Muell. Arg.	b	25	BA 22:22299
Aspidosperma excelsum Benth.	—	unn.	CA 49:1280
Aspidosperma megalocarpon Muell. Arg.	b	unn.	CA 48:13958
Aspidosperma oblongum A. DC.	—	unn.	CA 47:7109
Aspidosperma peroba Saldanha da Gama	b	25	Klein 792
Aspidosperma polyneuron Muell. Arg.	b	24	M-H II 422
Aspidosperma pyricollum Muell. Arg.	s	25	Klein 792
Aspidosperma quebracho Griseb.	b	23	Merck
	b	22, 25, 91, 120, 132	H 511
Aspidosperma quebracho-blanco Schlecht.	b	25	M-H II 422
	b	22	Merck
	b	23, 24, 52	Quart. Rev. 10:139
Aspidosperma quirandy Hassler	b	22, 25, 49, 92	M-H II 422
Aspidosperma sessiliflorum Muell. Arg.	l, b	25	Klein
Aspidosperma ulei Markgraf	—	unn.	CA 49:7730
Aspidosperma sp.	—	unn.	BA 23:1939
Aspidosperma spp.	b	78, 79	M-H II 422
Calpicarpum roxburghii G. Don	—	unn.	M-H V 315
Carissa ovata R. Br.	b	unn.	Webb 241
Cerbera ahouai L.	—	27	Sok 133
Chilocarpus australis F. Muell.	l	unn.	Webb 241
Chonemorpha macrophylla (Roxb.) G. Don	rb	31	CA 49:15926
Cyrtosiphonia madurensis Teijsm. and Binn.	—	unn.	We 985
Cyrtosiphonia spectabilis Miq.	—	unn.	Klein 741
Elytropus chilensis Muell. Arg.	l, s, r	unn.	CA 47:3519
Ervatamia angustisepala (R. Br.) Domin (Tabernaemontana orientalis var. angustisepala Benth.)	l, s	unn.	Webb 268

Species	Plant part	Alkaloids	References
Ervatamia orientalis (R. Br.) Turrill (Tabernaemontana orientalis R. Br.)	l, s	unn.	Webb 241
Ervatamia pubescens Markgraf	l	unn.	Webb 268
Ervatamia sp.	—	unn.	Webb PS
Forsteronia pubescens A. DC.	l	46a	Klein 795
Funtumia spp.	l, s, r	unn.	Wall 4
Geissospermum sericeum (Sag.) Benth. & Hook.	—	47	CA 49:4234
Geissospermum vellosii Allem.	b	47	H 735
	b	121	Klein 799
	—	82	Sok 129
	b	81	Klein 799
	b	81, 121	H 736
Gonioma kamassi E. Mey.	b	63	CA 45:9222
	—	unn.	H 781
Haplophyton cimicidum A. DC.	w	32, 48	CA 47:6594
Holarrhena africana A. DC.	b	35	H 742
Holarrhena antidysenterica (Roxb.) Wall.	b	33, 34, 35, 36, 37, 38, 50, 51, 57, 69, 70, unn. (2)	M-H V 313
	sd	76a	Klein 789
Holarrhena congolensis Stapf	b, l	35, 50	H 742
Holarrhena febrifuga Klotzsch	b	35	H 742
Holarrhena wulfsbergii Stapf	b	35	H 742
Hunteria corymbosa Roxb.	b	unn.	We 985
Hunteria eburnea Pichon	b	unn.	Compt. rend. 240:1470
Kickxia africana Benth.	sd	unn.	We Sup 113
Kickxia arborea Blume	b	unn.	We 988
Kopsia albiflora Boerl.	—	67	CA 48:1387
Kopsia arborea Blume	—	unn.	M-H V 315
Kopsia flavida Blume	—	67	Sok 129
	—	unn.	M-H V 315
Kopsia fruticosa (Ker) A. DC.	l	67	CA 44:2997
Kopsia longiflora Merrill	b	64, 66, 68	CA 50:1056
	l	65	CA 50:1056
Kopsia roxburghii Wehmer	sd	unn.	We 989
Kopsia sp. nov.	l, s	unn.	Webb 268
Leuconotis eugenifolius (Wall.) A. DC.	b	unn.	We 981
Lochnera (Vinca) lancea (Boj.) K. Schum.	l, s	136	CA 49:5496
Lochnera (Vinca) pusilla (Murr.) K. Schum.	—	126	Chopra 652
Melodinus acutiflorus F. Muell.	l, b	unn.	Webb 241
Melodinus australis Maiden and Betche	l, b	unn.	Webb 268

Species	Plant part	Alkaloids	References
Melodinus bacellianus (F. Muell.) S. T. Blake	l, b	unn.	Webb 268
Melodinus guilfoylei F. Muell.	l	unn.	Webb 268
Melodinus laevigatus Blume	l, b, sd	unn.	Chopra 653
Melodinus murpe F. M. Bailey	l	unn.	Webb 268
Nerium oleander L.	—	87a	Klein 741
Ochrosia ackeringae Miq.	b	unn.	We 989
Ochrosia acuminata Trimen	b	unn.	We 989
Ochrosia calocarpa Miq.	b	unn.	We 989
Ochrosia coccinea Miq.	b	unn.	We 989
Ochrosia cowleyi F. M. Bailey	l	unn.	Webb 268
Ochrosia elliptica Labill.	b	unn.	H 781
Ochrosia kilneri F. Muell.	l	unn.	Webb 268
Ochrosia moorei F. Muell.	l, b	unn.	Webb 268
Ochrosia poweri F. M. Bailey	l, s, b	unn.	Webb 241
Ophioxylon serpentinum L. (Rauvolfia s.)	rb	unn.	We 981
Ophioxylon trifoliatum Gaertn. (Rauvolfia s.)	rb	unn.	We 981
Parsonsia buruensis (Teijsm. and Binn.) Boerl.	b, wd	unn.	Webb 268
Parsonsia eucalyptifolia F. Muell. (Lyonsia eucalyptifolia F. Muell.)	l, s	unn.	Webb 241
Parsonsia latifolia (Benth.) S. T. Blake	l, b	unn.	Webb 268
Parsonsia lilacina F. Muell.	l, s	unn.	Webb 268
Parsonsia minahassae Koord.	l, b	unn.	We 981
Parsonsia straminea F. Muell.	l, b	unn.	Webb 268
Parsonsia velutina R. Br.	l, s	unn.	Webb 241
	fl	unn.	Webb 268
Picralima klaineana Pierre	sd	6, 7, 8, 9, 10, 11, 12, 13	H 760
	sd	86, 87	M-H V 320
Picralima nitida Th. & H. Dur.	sd	7, 9, 10, 13, 86, 87	CA 46:2556
	—	11	Quart. Rev. 10:141
Prestonia amazonica (Benth.) Macbr. (Haemadictyon a.)	—	131a, 131b	US Disp. 24, 1651
Pseudochrosia glomerata Blume	b	unn.	We 989
Rauvolfia beddomei Hook. f.	r	105, 136	J. Indian Chem. Soc. 33:379
Rauvolfia caffra Sond.	r	4	Quart. Rev. 10:129

Species	Plant part	Alkaloids	References
Rauvolfia cambodiana Pierre ex Pitard	rh	unn.	Compt. rend. 244:1254
Rauvolfia canescens L.	r	2, 4, 104, 105	Naturw. 42:39
	l	21, 60, 61, 102, 133, 134	CA 49:10320
	r	26	JACS 77:820
	—	40	CA 49:10511
	r	41	JAPA 45:89
	r	59, 95	JAPA 44:639
	—	103	JAPA 253
	r	88	JCS 1956:187
	r	89	CA 49:10321
	r	93a	JOC 21:923
	l	99	CA 35:7967
	r	100	CA 50:4994
	r	108	CA 49:11956
	r	132	Naturw. 41:47
	r	137	Quart. Rev. 10:129
Rauvolfia cumminsii Stapf	rb	103	CA 50:5991
Rauvolfia densiflora Benth.	r	4, 103	Naturw. 42:182
Rauvolfia grandiflora Mart.	rb	103, unn.	CI 1956:173
Rauvolfia hirsuta Jacq.	r	19	CA 49:11239
	r	105	CA 50:2745
Rauvolfia heterophylla Willd.	r, l, s	2, 4, 21, 99, 108, 132	JACS 77:3551
	l, b, wd	28, 29	CA 32:721
	r	103	Naturw. 42:182
Rauvolfia indecora Woodson	r	105	J. Indian Chem. Soc. 33:381
Rauvolfia inebrians K. Schum.	r, b	unn.	CA 51:6952
Rauvolfia mannii Stapf	r	103	:8896
Rauvolfia micrantha Hook. f.	—	2, 103	CA 49:9229
	—	75a, 107a	Schl 56
Rauvolfia mombasiana Stapf	r	103	CI 1956:1387
Rauvolfia nana E. A. Bruce	r	103	CA 51:8896
Rauvolfia natalensis Sond.	rb	4, 103	JCS 1956:215
	b	97	We Sup 172
Rauvolfia obscura K. Schum.	—	19	Quart. Rev. 10:129
Rauvolfia perakensis King and Gamble	r	80, 103	Naturw. 42:182
Rauvolfia sarapiquensis Woodson	—	103	CI 1956:1387

Species	Plant part	Alkaloids	References
Rauvolfia sellowii Muell. Arg.	rb	2, 3, 21, 103, 115, 116	JACS 77:6687
	rb	4, 5, 108	CA 49:14270
Rauvolfia semperflorens (Muell. Arg.) Schlecht.	b	106	CA 49:3218
Rauvolfia serpentina (L.) Benth.	r	2, 4, 5, 108, 109	CA 26:1288
	r	14, 15	JACS 76:3234
	r	16, 56, 75, 76, 104, 135	Quart. Rev. 10:129
	r	30	CA 49:4938
	r	58, 93	CA 49:2447
	r	62a	CA 49:9666
	r	74, 77, 118, 132	CA 49:4684
	r	98	CA 48:1380
	r	101	JACS 77:2241
	r	102	CA 49:5778
	r	103	CA 47:8084
	r	105	CA 49:1742
	r	110	CA 49:5494
	r	111	CA 50:532
	r	46	CA 50:2622
	—	96	CA 48:6649
	r	unn. I, II	CA 48:9626
	r	136	CI 1954:375
Rauvolfia ternifolia HBK. (R. ligustrina Roem. and Schult.)	r	103	CA 51:670
Rauvolfia tetraphylla L.	r	103, 109, 116, 117	CI 1955:627
Rauvolfia verticillata Baill.	b	136	CA 50:8965
Rauvolfia vomitoria Afzel.	r, rb	2, 4, 19, 56, 94, 103,107	AJP 127:270
	r	101	CA 49:16337
	rb	60, 105	CA 51:6085
Rejoua sp.	—	unn.	Webb PS
Rhynchodia macrantha Wehmer	b	unn.	We 985
Strophanthus gratus Baill.	sd	119	Klein 294
Strophanthus hispidus DC.	sd, rb	119	Klein 294
Strophanthus kombe Oliver	sd	119	M-H I 176
Tabernaemontana coronaria (Jacq.) R. Br.	b	39, 112	H 501
Tabernaemontana crispa Roxb.	rb	unn.	CA 49:6541
Tabernaemontana dichotoma Roxb.	b	unn.	CA 48:7715
Tabernaemontana salzmanni A. DC.	l, b, fr	112	We 986

Species	Plant part	Alkaloids	References
Tabernaemontana sphaerocarpa Blume	l, b, fr	112	Klein 799
Tabernaemontana wallichiana Steud.	b	112	We 986
Tabernanthe iboga Baill.	r	53, 113	H 768
	r	54	BA 26:19313
	—	55	CA 47:8969
Tanghinia venenifera Poir.	—	114a	Klein 741
Tonduzia longifolia (A. DC.) Markgraf	r	4, 40, 101, 103	JOC 21:480
Urechites lutea (L.) Britt.	l, s, fr	unn.	Authors' lab.
Vallesia dichotoma Ruiz and Pav.	—	25, 120	M-H II 422
Vallesia glabra (Cav.) Link	l, s	25, 120	M-H II 422
Vinca difformis Pourr.	—	124a	CA 50:17338
Vinca herbacea Waldst. and Kit.	—	unn.	CA 27:1029
Vinca major L.	l, s	104, 111	CA 49:11672
	—	13	CA 49:8563
	—	124	CA 49:16343
	—	123	CA 50:8694
Vinca minor L.	l	62	Monatsh. 85:10
	—	83	CA 49:10328
	—	90, 128	Sok 129
	l	125	Helv 36:2017
	—	127	M-H V 328
	l	unn.	Wall 4
Vinca pubescens Urv.	l	90, 128	H 778
Vinca (Lochnera) rosea L.	—	125	CA 50:4985
	r, l	2	CA 48:4559
	r, b	71, 108	CI 1956:173
	l, s	unn.	Webb 241
	r	13	Compt. rend. 245:1789
Voacanga africana Stapf	r, b	129, 131	CA 49:12774
	b	130	CA 49:12775
Voacanga bracteata Stapf	s	130a	Compt. rend. 244:1955
Voacanga foetida (Blume) K. Schum.	b	unn.	We 985
Voacanga obtusa K. Schum.	r, b	129, 131	CA 49:12774
	b	130	CA 49:12775
Voacanga thouarsii Roem. and Schult.	b	130	CA 50:8965
Voacanga sp.	—	unn.	Webb PS
Wallichiana sp.	—	unn.	Klein 741
Wrightia antidysenterica (L.) R. Br.	sd, b	35	Klein 676
Wrightia millgar F. M. Bailey	b	unn.	Webb 241
Wrightia zeylanica (L.) R. Br.	—	35	Sok 129

TABLE 2

ALKALOIDS OCCURRING IN THE APOCYNACEAE

1. abyssinine
2. ajmalicine (vinceine, vincaine, δ-yohimbine)
3. ajmalidine
4. ajmaline (rauwolfine I. and S.)
5. ajmalinine
6. akuammenine
7. akuammicine
8. ψ-akuammicine
9. akuammidine
10. akuammigine
11. ψ-akuammigine
12. akuammiline
13. akuammine (vincama joridine)
14. Alkaloid A (ex Rauvolfia serpentina)
15. alkaloid F
16. alloyohimbine

16a. alstonamine

17. alstonidine
18. alstoniline
19. alstonine
20. amsonine
21. aricine
22. aspidosamine
23. aspidospermatine
24. aspidospermicine
25. aspidospermine
26. canescine
27. carpaine
28. chalchupine A
29. chalchupine B
30. chandrine
31. chonemorphine
32. cimicidine
33. conessidine
34. conessimine
35. conessine
36. conimine
37. conkurchine
38. conkurchinine
39. coronarine
40. deserpidine
41. 11-desmethoxyreserpine
42. ditamine
43. echitamidine
44. echitamine
45. echitenine
46. 3-epi-α-yohimbine

46a. forsteronine

47. geissospermine
48. haplophytine
49. haslerine
50. holarrhenine
51. holarrhimine
52. hypoquebrachine
53. ibogaine
54. ibogamine
55. iboluteine
56. isoajmaline
57. isoconessimine
58. isorauhimbine
59. isoraunescine
60. isoreserpiline
61. isoreserpinine
62. isovincamine

62a. isoyohimbine

63. kamassine
64. kopsamine
65. kopsiflorine
66. kopsilongine
67. kopsine

68. kopsinine
69. kurchicine
70. kurchine
71. lochnerine
72. macralstonidine
73. macralstonine
74. 11-methoxy-δ-yohimbine
75. methyl reserpate
75a. micranthine
76. neoajmaline
76a. norconessine
77. papaverine
78. paytamine
79. paytine
80. perakenine
81. pereirine
82. pereitrine
83. perivincine
84. porphyrine
85. porphyrosine
86. pseudoakuammicine
87. pseudoakuammigine
87a. pseudocurarine (?)
88. pseudoreserpine
89. pseudoyohimbine
90. pubescine
91. quebrachamine
92. quirandine
93. rauhimbine (corynanthine)
93a. raujemidine
94. raumitorine
95. raunescine
96. raupine
97. rauwolfine
98. rauwolfinine
99. rauwolscine (α-yohimbine)
100. recanescine
101. rescinnamine
102. reserpiline
103. reserpine
104. reserpinine
105. sarpagine
106. semperflorine
107. seredine
107a. serpentidine
108. serpentine
109. serpentinine
110. serpine
111. serpinine
112. tabernaemontanine
113. tabernanthine
114. tabersonine
114a. tanghinine
115. py-tetrahydroalstonine
116. tetraphyllicine
117. tetraphylline
118. thebaine
119. trigonelline
120. vallesine
121. vellosine
122. villalstonine
123. vincamajine
124. vincamajoreine
124a. vincamedine
125. vincamine
126. vincarosine
127. vineamine
128. vinine
129. voacamine
130. voacangine
130a. voacorine
131. vobtusine
131a. yageine (harmine?)
131b. yagenine (harmine?)
132. yohimbine
133. α-yohimbine (rauwalscine)
134. β-yohimbine
135. γ-yohimbine
137. ψ-yohimbine
136. δ-yohimbine (ajmalicine)

DRUG INFORMATION SOURCES

(Yugoslavia, Turkey, Israel, Egypt)

YUGOSLAVIA

Gotovi Lekovi. 3d ed. Belgrade, Medicinska Knjiga, 1956. 577 pp. 680.- Din.

An official (government) compilation of information about drug specialties and biologicals. In the second edition (1950), which is the latest edition available to the Committee, information about specialties includes manufacturer, composition, indications, dosage, forms and sizes and alternate names (or equivalent drugs, as Synkayvit for Kavitamin "Galenika"). A therapeutic index and an alphabetic index are also included. It is noted that the third edition is considerably expanded over the second edition, which had only 167 pages.

Receptni Priručnik, by Dragutin Tomić. Belgrade, Medicinska Knjiga, 1956. 269 pp. 650.- Din.

A prescribing handbook for physicians. Drugs are grouped in chapters according to pharmacologic action. Individual chapters list official drugs with their therapeutic and maximal dosages, formulas for mixtures and specialty drugs. For specialties, composition, manufacturer's name, forms and sizes are given. A list of manufacturers with their addresses and a therapeutic index are also included. The general alphabetic index includes all drug names.

Farmakoterapija; Priručnik za Prakticnog Lijecnika i Medicinara, by Ivo Ivančević and Radovan Damaska. 3d ed. Belgrade, Medicinska Knjiga, 1952. 364 pp. 480.- Din.

A manual for physicians in several parts. The text includes both pharmacologic and therapeutic indexes to drugs, a list of official drugs (Latin or English names) with their alternate names, a table of incompatibilities and a list of definitions of standard units for vitamins, biologicals, etc. A section entitled "Materia medica" provides an

alphabetic list of drugs with their actions, indications, dosages and possible side effects and contraindications. The final chapters are arranged according to indications and provide formulas for remedies to be used in the conditions listed. All drug names are included in the general alphabetic index.

Synonyma Pharmaceutica, by Josip Hofman. Farmaceutsko Drustvo Hrvatske, 1954. 338 pp. 1,200.- Din.

An alphabetic list of 2788 drug products with all known alternate names (including proprietary and chemical names). All drug names, including chemical names, appear in a separate alphabetic index.

Terapijske Doze i Oblici Lijekova, by Dragutin Tomić. 3d ed. Zagreb, Nakladni Zavod Hrvatske, 1950. 116 pp. 85.- Din.

An alphabetic list of drug products, including specialties, giving therapeutic and maximal doses for their various forms and also reporting briefly their pharmacologic actions. For specialties a brief statement of composition is included. Cross references from generic to proprietary names (and vice versa) are given.

Uvod u Galensku Farmaciju, by Jaroslav Ječmen. Zagreb, Školska Knjiga, 1955. 2 vols. (308 pp.) 690.- Din.

A textbook for pharmacy students, arranged by pharmacologic groups. Composition, manufacturer and forms supplied are reported.

Farmakografija; Nauka o Propisivanju Lijekova, by Ivo Ivančević and Dragutin Tomić. 3d ed. Zagreb, Nakladni Zavod Hrvatske, 1951. 228 pp. 450.- Din.

A pharmacology textbook and compilation of information about the actions of drugs. In Part II, chapters are arranged according to form, i.e., solutions, injections, tablets, etc., and in Part III, according to pharmacologic action. Formulas for drug preparations appear throughout the text and specialties of pharmaceutical houses are named when they are equivalent or nearly so. An alphabetical list of drugs, with their effective dosages, a table of solubilities and a

therapeutic index are included. All drug names appear in the general alphabetic index.

Ad Usum Veterinarium, by B. Krajinovic. Belgrade, Vetprom, 1950. 354 pp.

This is an alphabetic list of veterinary products (Yugoslav and foreign). Information about individual products includes composition, action, indications, dosage, manufacturer and forms supplied.

Compiler's note: Manufacturers of pharmaceutical specialties in Yugoslavia publish trade lists containing product descriptions and summaries of actions and indications. The three major manufacturers and titles of the latest lists referred to the Committee are the following:

Farmaceutski Proizvodi, 1955. Alphabetic list of specialties of the factory Galenika in Zemun, Yugoslavia.

Vademecum, 1954. Alphabetic list of specialties of the factory Pliva, in Zagreb.

Koledarcek, 1955. Alphabetic list of specialties of the factory Lek in Ljubljana, Yugoslavia.

TURKEY

Yabanci Tibbi Müstahzarlar (Farmakodinamik Esaslara Göre), by Dr. Saib Ragib Atademir. Konya, Atademir Yayimevi, 1949. 531 pp. + advertising matter.

A compilation of information about specialty drugs. The text is divided into groups according to therapeutic indications or pharmacologic actions. Within each group specialties are listed according to composition, with information about manufacturer, composition, forms and sizes, actions, indications, and dosage. A full chapter is devoted to antibiotics and sulfonamides and their comparative action in various diseases. All drug names are included in the general alphabetic index.

Türkiye Eczacilar Almanagi 1949, by Remzi Kocaer. Istanbul, Hüsnütabiat Basimevi, 1949. 447 + xxxii pp. + advertising matter.

A pharmaceutical almanac, giving information about history, schools, laws and associations of pharmacy in Turkey and activities of Turkish pharmacists. Turkish laboratories with their products are listed on pages 181-213, laboratories of pharmacies with their products on pages 213-221 and foreign manufacturers and Turkish representatives of foreign manufacturers with their products on pages 239-255. There is no general alphabetic index to products in these sections. There is a 32-page summary in English of the entire text.

Tibbi Formüller ve Tedavi Esaslari, by Dr. Saib Ragib Atademir. Konya, 1950. 462 pp.

A handbook on drugs for the physician. Drugs are grouped according to pharmacologic action; both formulas for remedies and names of specialties are provided. Information about specialties includes both name of manufacturer and composition. A detailed therapeutic index is also provided. The general alphabetic index does not include all specialty names.

ISRAEL

Index of Medicines Produced in Israel, by Dr. J. M. Aladjemoff. Jerusalem, 1953. 492 pp. $5.00.

A compilation of information about pharmaceutical specialties of Israel. Preparations are listed alphabetically by proprietary name. Information includes composition, indications, dosage and packing. An abbreviated manufacturer's name is given for each product, but no addresses are given. Available from the author at X-Ray Institute, 28, David Yellin Road, Jerusalem. [Reference is made to a second book by the same author, *Therapeutic Index;* the Committee on Drug Information Sources has not yet obtained a copy of this publication.]

EGYPT

Egypt and the Middle East Medical Index. 1st ed. Cairo, 1957. Four separately paged sections (851 pp.)

This new compilation appears to be an expansion of the *Index Medical et Pharmaceutique d' Egypte,* published by the Middle East Publishing Co. in 1954. Part I of the present compilation is an alphabetic list of medical specialties marketed in Egypt with name of manufacturer, composition, indications, contraindications, administration, dosage and packing. Part II is an alphabetic list of local and foreign laboratories represented in Egypt with their products and names of their agents. Part III lists products according to their major constituents or their pharmacologic effects and Part IV is an index to products according to diseases in which they are indicated. The text is entirely in English. Publisher's address: 29, Abdel Khalek Saroit Street, Cairo and 5, Rue, de l'Ancienne Bourse, Alexandria.

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SELECTED ABSTRACTS

Studies on the Absorption and Excretion of Sulfamethoxypyridazine. Nichols, R. L. and Finland, M. *J. Lab. and Clin. Med. 49*:410 (1957). The new antibacterial sulfonamide, sulfamethoxypyridazine (3-sulfanilamido-6-methoxypyridazine), had been shown by laboratory tests on animals to have high solubility in urine, good absorption from the gastrointestinal tract, good penetration into the cerebrospinal fluid, and an antibacterial activity equal to that of sulfadiazine. These findings warranted the trial of the drug in human beings. Therefore, the authors administered 3.0 Gm. in a single oral dose to six normal young men and repeated doses of 1 Gm. every 48 hours to 7 patients. The absorption and excretion of the drug were studied.

After a dose of 3 Gm., maximum plasma levels of nearly 26 mg. per 100 ml. were noted within about 7 hours. These levels gradually decreased to insignificant levels during the subsequent 8 days or longer. Nearly all of the drug was recovered in the urine, about one-half of which was in the conjugated form. Detectable amounts of the sulfonamide were demonstrable in the urine 10 to 14 days after the single oral dose.

Increasing the intake of fluid had no appreciable effect upon the excretion of the drug. The oral administration of alkalis for short periods produced only a slight increase in the rate of excretion. However, a definite increase in the clearance of the drug from the plasma was found to accompany the diuresis and alkalinization of the urine that followed the ingestion of 0.5 Gm. of acetazolamide.

The continuous administration of 1 Gm. every other day produced plasma concentrations which would generally be considered to be optimum, comparable to those found in patients given 1 Gm. of sulfadiazine every 4 to 6 hours. However, the concentrations of sulfamethoxypyridazine in the urine were lower but significant.

The only side effect noted from the administration of this new, long-acting sulfonamide was a moderately severe headache in most of the subjects who received the 3 Gm. dose. No untoward effects were experienced by the patients receiving repeated doses of 1 Gm. every 48 hours.

The Effect of a Stannous Fluoride Dentifrice in Preventing Decay and Loss of Teeth in Children. Jordan, W. A. and Peterson, J. K. *J. Am. Dent. Assoc. 54:*589 (1957). Stannous fluoride has been shown to be more effective than sodium fluoride in reducing dental caries in animals and in human children. The value of stannous fluoride in a dentifrice has also been investigated but further verification of its value in practice was needed. Therefore, the authors undertook a study involving 628 children between the ages of 5 and 11. Two paste dentifrices were employed, one for the children in one school and the other for the children in another school. Neither the children nor the dentist knew which paste contained the stannous fluoride. The stannous fluoride paste had a pH of 4.9 and the following formula:

Heat-treated calcium orthophosphate	39.00
Detergent	1.51
Humectant	30.00
Binder	1.50
Stannous pyrophosphate	1.00
Stannous fluoride	0.40
Flavor, etc.	1.62
Water	24.97

The other paste differed only in that it did not contain either of the stannous salts and had a pH of 6.8. The low pH of the stannous fluoride paste was necessary for stability and effectiveness of the stannous fluoride.

The children were encouraged to brush their teeth after every meal. This was done under supervision at school after the noon meal. By checking the amount of dentifrice used it was found that both groups of children were using essentially the same amount.

After one year of this controlled study, it was found that 35 per cent fewer missing or filled teeth developed among the children using the stannous fluoride dentifrice than in the control group. This reduction was statistically significant. The prevalence of stained teeth in both groups was about equal, 40 children in the group using the stannous fluoride dentifrice and 45 in the control group. The fluoride content of the urine of 40 boys from each group was determined after more than half of the study year had passed. It was found that the fluoride concentration was 0.198 ppm in the urine of the boys using the stannous fluoride paste and 0.196 ppm in the control group.

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